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Remarks:
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(54) Improved process for producing moxonidine

(57) The present invention provides improved process for production of highly pure Moxonidine comprising reacting the starting material 6-dichloro-2-methyl-5-(1-acetyl-2-imidazolin-2-yl)-aminopyrimidine (DMAIA) with different bases (e.g., sodium hydroxide or potassium hydroxide), thus avoiding the use of sodium methoxide while carrying out the reaction at milder conditions. While using sodium methoxide, is not needed to use methanol as solvent and a more friendly class 3 solvent (e.g., DMSO) is used instead. The reaction may be carried out at ambient temperature and it is not necessary to use two-fold excess of the base as about 1.0-1.1 molar excess of sodium methoxide in relation to DMAIA is sufficient.

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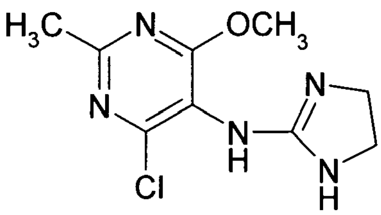
Description

FIELD OF THE INVENTION

[0001] The present invention relates to the field of organic chemistry and more particularly to improved process for producing Moxonidine.

BACKGROUND OF THE INVENTION

[0002] Moxonidine (4-chloro-5-(imidazoline-2-ylamino)-6-methoxy-2-methylpyrimidine), has the structural formula (I) below and is used as an antihypertensive drug.

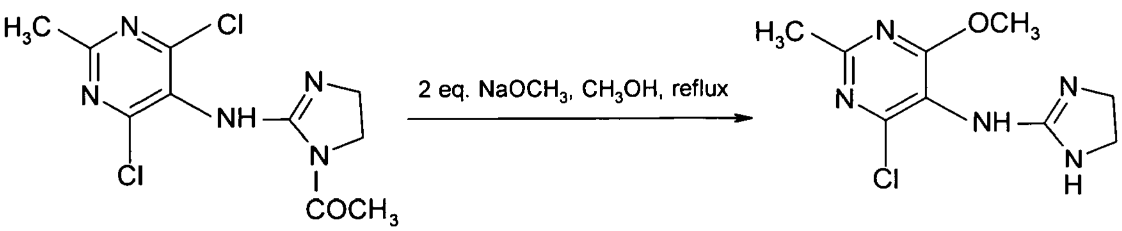


(I)

[0003] Moxonidine was approved for use in Germany in 1991 and is currently commercially available in Europe, e.g., in Germany, Austria and the UK.

[0004] U.S. patent No. 4,323,570 (hereinafter the '570 patent) describes a method of preparing Moxonidine (I) by reacting 4,6-dichloro-2-methyl-5-(1-acetyl-2-imidazolin-2-yl)-aminopyrimidine (hereinafter DMAIA) of formula (II) with about 2 equivalents of sodium methoxide in methanol under reflux, as depicted in Scheme 1.

Scheme 1



(II) (I)

[0005] According to example 3 of the '570 patent, Moxonidine is obtained by crystallization from nitromethane.

[0006] Czech patent No. 294649 (hereinafter the '649 patent) describes a method of preparing Moxonidine from DMAIA by methanolysis reaction using alkali metal carbonates e.g., potassium carbonate at 47-52°C or sodium bicarbonate at 65°C.

[0007] The teaching of European patent applications titled "Novel polymorphs of Moxonidine and processes for preparation therefor" and "Novel purification process of Moxonidine" by the present applicant, filed concurrently on even date are incorporated herein by reference.

[0008] Boiling sodium methoxide is highly corrosive and toxic and therefore there is a need in the art for an improved process for preparing Moxonidine that will use less toxic and corrosive reagents, e.g., sodium hydroxide and potassium hydroxide at a considerably lower concentration (e.g., 1 mole equivalent instead of 2 mole equivalents), and using lower reaction temperatures.

SUMMARY OF THE INVENTION

[0009] The inventors of the present invention have discovered that it is not needed to use sodium methoxide for converting 4,6-dichloro-2-methyl-5-(1-acetyl-2-imidazolin-2-yl)-aminopyrimidine (DMAIA) into Moxonidine as other more user-friendly bases, e.g., sodium hydroxide and potassium hydroxide may be used instead in much milder conditions (ambient temperature and relatively low molar excess of the base). However, in the event the use of sodium methoxide is still desired, it is not needed to use methanol as solvent and a more friendly class 3 solvent (e.g., DMSO) may be used instead. Furthermore, the reaction may be carried out at ambient temperature and it was surprisingly discovered that is not necessary to use two-fold excess of the base as about 1.1 molar excess of the base, e.g., sodium hydroxide in relation to DMAIA is sufficient.

[0010] The present invention provides an improved process for producing Moxonidine of formula (I) in a high purity and yield, the process comprising:

reacting DMAIA with a non-methoxide base in methanol;

diluting the reaction mixture with water;

isolating Moxonidine; and

optionally purifying Moxonidine by crystallization.

[0011] Preferably, the non-methoxide base is selected from sodium hydroxide, potassium hydroxide, lithium hydroxide, cesium hydroxide, potassium carbonate, sodium carbonate, lithium carbonate, cesium carbonate, potassium bicarbonate, sodium bicarbonate, lithium bicarbonate, cesium bicarbonate, and a combination thereof.

[0012] The present invention provides an alternative improved process for producing Moxonidine of formula (I) in high purity and yield, the process comprising:

reacting DMAIA with sodium methoxide in an organic solvent at ambient temperature;

quenching the reaction mixture with water;

isolating Moxonidine; and

optionally purifying Moxonidine by crystallization.

[0013] According to one embodiment of the present invention, the organic solvent is selected from the group consisting of methanol, tetrahydrofuran (THF), toluene, dimethyl sulfoxide (DMSO), and a mixture thereof.

[0014] The present invention also provides a more convenient and environmentally friendly process for purifying Moxonidine by crystallization, wherein the solvent used is other than nitromethane, the process comprising:

mixing the crude Moxonidine with an organic solvent;

heating to an elevated temperature;

allowing the mixture to cool sufficiently to enable crystallization; and

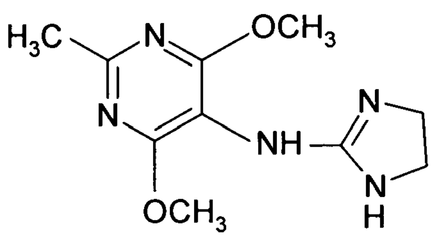
isolating the crystals, washing and drying.

[0015] According to another embodiment of the present invention, the crude Moxonidine is obtained by the process described herein in at least 88% overall yield, preferably in a yield higher than 90.5%. The crystallized Moxonidine is obtained having a purity of at least 98%, preferably having a purity equal to or greater than 99.5%, and more preferably having a purity equal to or greater than 99.8%.

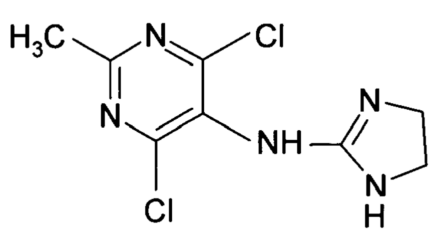
DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0016] The inventors of the present invention have discovered that it is not needed to use sodium methoxide for converting 4,6-dichloro-2-methyl-5-(1-acetyl-2-imidazolin-2-yl)-aminopyrimidine (DMAIA) into Moxonidine as other more user-friendly bases, e.g., sodium hydroxide and potassium hydroxide may be used instead in much milder conditions (ambient temperature and relatively low molar excess of the base). However, in the event the use of sodium methoxide is still desired, it is not needed to use methanol as solvent and a more friendly ICH class 3 solvent (e.g., DMSO) may be used instead. Furthermore, the reaction may be carried out at ambient temperature and it was surprisingly discovered that it is not necessary to use two-fold excess of the base and about 1.1 molar excess of the base, e.g., sodium hydroxide in relation to DMAIA is sufficient.

[0017] While searching for an improved process for preparing Moxonidine, the inventors of the present invention have reproduced example 3 of the '570 patent and example 1 of the '649 patent and found that in both cases the crude Moxonldine contained substantial levels of the impurities 4,6-dimethoxy-2-methyl-5-(2-imidazolin-2-yl)-aminopyrimidine of formula (III) and 4,6-dichloro-2-methyl-5-(2-imidazolin-2-yl)-aminopyrimidine of formula (IV), as described in reference examples 1 and 2 respectively.



(III)



(IV)

[0018] It is apparent to those skilled in the art that purifying crude Moxonidine from these impurities, namely compounds (III) and (IV), may not an easy task to achieve, and the purified Moxonidine is liable to be obtained in a relatively low yield. Therefore, there is a need in the art for an improved process for producing Moxonidine in high purity and yield, wherein the content of the impurities is minimal.

[0019] The present invention provides such an improved process for producing Moxonidine, the process comprising:

reacting DMAIA with a non-methoxide base in methanol;

diluting the reaction mixture with water;

isolating Moxonidine; and

optionally purifying Moxonidine by crystallization.

[0020] Preferably, the non-methoxide base is selected from sodium hydroxide, potassium hydroxide, lithium hydroxide, cesium hydroxide, potassium carbonate, sodium carbonate, lithium carbonate, cesium carbonate, potassium bicarbonate, sodium bicarbonate, lithium bicarbonate, cesium bicarbonate, and a combination thereof.

[0021] According to one embodiment of the present invention, methanol is used as a solvent and the volume of methanol is 4-12 ml relative to 1 g of DMAIA, preferably the volume of methanol is 8 ml relative to 1 g of DMAIA.

[0022] According to another embodiment of the present invention, a non-methoxide base is used in the reaction and the amount of this base is lower than 2 mole equivalents per one mole equivalent of DMAIA.

[0023] According to one aspect of this embodiment of the present invention, the amount of the non-methoxide base, e.g., potassium carbonate is between about 0.6 - 1.0 molar equivalents relative to one mole of DMAIA.

[0024] According to another aspect of this embodiment of the present invention, the amount of the non-methoxide base, e.g., sodium hydroxide is between about 1.1-1.5 equivalents relative to one mole of DMAIA.

[0025] According to yet another aspect of this embodiment of the present invention, the amount of the non-methoxide base, e.g., potassium hydroxide is between about 1.1-1.7 equivalents relative to one mole of DMAIA.

[0026] According to yet another aspect of this embodiment of the present invention, the amount of the non-methoxide base, e.g., sodium bicarbonate is between about 1.0-1.7 equivalents relative to one mole of DMAIA.

[0027] According to yet another aspect of this embodiment of the present invention, the amount of the non-methoxide base, e.g., potassium bicarbonate is about 1.5 equivalents relative to one mole of DMAIA.

[0028] According to yet another aspect of this embodiment of the present invention, a small amount of water may be added to the mixture containing sodium bicarbonate or potassium bicarbonate e.g., 1 ml per 20 ml of the solvent.

[0029] According to yet another aspect of this embodiment of the present invention, the reaction may be carried out using a combination of bases, e.g. potassium hydroxide and potassium carbonate.

[0030] The present invention provides an alternative improved process for producing Moxonidine, the process comprising:

reacting DMAIA with sodium methoxide at ambient temperature in an organic solvent;

quenching the reaction mixture with water;

isolating Moxonidine; and

optionally purifying Moxonidine by crystallization.

[0031] According to another embodiment of the present invention, the organic solvent used in the reaction is selected from the group consisting of methanol, tetrahydrofuran (THF), toluene, dimethyl sulfoxide (DMSO), and mixtures thereof.
[0032] According to yet another embodiment of the present invention, the volume of tetrahydrofuran (THF), toluene, or dimethyl sulfoxide (DMSO) is about 10 ml relative to 1 g of DMAIA.
[0033] According to yet another embodiment of the present invention, sodium methoxide is used in the reaction and the amount of sodium methoxide is about 0.9-1.7 equivalents relative to one mole of DMAIA, preferably 1.1 equivalents.
[0034] According to yet another embodiment of the present invention, the reaction may be carried out at any temperature in the range of 0°C and reflux. Preferably, the temperature for carrying out the reaction is between ambient temperature and 2-5 50°C, and more preferably the temperature for carrying out the reaction is ambient temperature.
[0035] According to yet another embodiment of the present invention, the reaction may be stopped after most of the unwanted intermediate 4,6-dichloro-2-methyl-5-(2-imidazolin-2-yl)-aminopyrimidine of formula (IV) has disappeared, as monitored by HPLC.
[0036] According to yet another embodiment of the present invention, after reaction completion, water is added to the reaction mixture and crude Moxonidine is isolated from the resulting suspension by filtration. The crude Moxonidine is then washed 5 with water and with 2-propanol and dried.
[0037] The present invention also provides a process for purifying Moxonidine by crystallization, wherein the solvent used is other than nitromethane, the process comprising:

mixing the crude Moxonidine with a solvent;

heating to an elevated temperature;

allowing the mixture to cool sufficiently to enable crystallization; and

isolating the crystals, washing and drying.

[0038] Typically, the crystallization solvent is a class 3 solvent, e.g., acetone, 1-propanol, 2-propanol, 1-butanol, 2-butanol, dimethyl sulfoxide (DMSO), and a mixture thereof.
[0039] According to yet another embodiment of the present invention, the crude Moxonidine is obtained by the process described herein in at least 88% overall yield, preferably in a yield higher than 90.5%. The crystallized Moxonidine is obtained having a purity of at least 98%, preferably having a purity equal to or greater than 99.5%, and more preferably having a purity equal to or greater than 99.8%.

Examples

[0040] HPLC measurements of Moxonidine samples were performed using HPLC system, equipped with Phenomenex Luna 5μ C8(2) (4.6 x 250 mm) column, and a UV detector operated on 230 nm. Analyses were performed using the following mobile phase, at flow rate of 1.2 ml/minute. Eluent A: 10 mM pentanesulfonic acid, pH = 3.0 with H_2SO_4. Eluent B: acetonitrile. Gradient (A/B, v/v): 0 min (94/6), 4 min (94/6), 20 min (64/36), 50 min (64/36).

Reference Example 1 - Preparation of Moxonidine by reaction of 4,6-dichloro-2-methyl-5-(1-acetyl-2-imidazolin-2-yl)-aminopyrimidine (DMAIA) with 2.02 equivalents of sodium methoxide at boiling temperature

[0041] 4,6-dichloro-2-methyl-5-(1-acetyl-2-imidazolin-2-yl)-aminopyrimidine (10 g, 0.0347 mol) was mixed with a solution of sodium methoxide (3.78 g, 0.07 mol, 2.02 equiv.) in 35 ml of methanol and boiled for 2 hours. Then, water (100 ml) was added and the reaction mixture was cooled to ambient temperature. A colorless product was collected by filtration, washed with water and dried at 50° C overnight to yield crude Moxonidine containing 6.5% of impurity (III) and

0.61 % of impurity (IV).

Reference Example 2 - Preparation of Moxonidine by reaction of DMAIA with 2 molar equivalents of potassium carbonate at 47-52° C.

[0042] Potassium carbonate (9.6 g, 0.0694 mol, 2 molar equiv.) was added to a suspension of DMAIA (10 g, 0.0347 mol) in methanol (80 ml) and the mixture was heated at 47-52° C for 5 hours. Then, the reaction mixture was cooled to ambient temperature and acetic acid (10 ml) and water (70 ml) were added. After stirring for half an hour, 25% solution of ammonium hydroxide (10 ml) was added and the mixture was stirred for one hour. A colorless precipitate was collected by filtration, washed with water and dried at 50° C overnight to yield crude Moxonidine containing 0.07% of impurity (III) and 0.40% of impurity (IV).

Example 1 - Preparation of Moxonidine by reaction of DMAIA with 1.1 equivalents of sodium methoxide at ambient temperature

[0043] Sodium methoxide (25% solution in methanol, 7.7 ml, 0.0382 mol, 1.1 equiv.) was added at ambient temperature to a suspension of DMAIA (10 g, 0.0347 mol) in methanol (50 ml) and the reaction mixture was stirred at ambient temperature for 24 hours. Then, water (100 ml) was added and the reaction mixture was cooled to ambient temperature. A colorless product was collected by filtration, washed with water (3 x10 ml) and 2-propanol (3 x10 ml) and dried at 50° C overnight to give 7.4 g of crude Moxonidine in 88.3% yield, having a purity of 99.17% (by HPLC), containing 0.04% of impurity (III) and 0.71% of impurity (IV).

Examples 2 - 9

[0044] The same reaction, which is provided in example 1, was carried out using sodium methoxide in methanol at different reaction conditions, or alternatively using other solvents than methanol, as depicted in Table 1

Table 1 - ***Preparation of crude Moxonidine by reaction of DMAIA with sodium methoxide in methanol and other solvents***

Ex No	DMAIA, g (mol)	Solvent, (ml)	Base, (mol, equiv.)	Temp., °C	Time, *h*	Crude yield g (%)	Purity, %	% of (III)	% of (IV)
2	10 (0.035)	MeOH (50)	CH_3ONa (0.035, 1.0)	25	24	7.4 (88.3)	98.27	0.02	1.56
3	10 (0.035)	MeOH (100)	CH_3ONa (0.059,1.7)	25	18	7.25 (86.5)	99.5	0.06	0.44
4	10 (0.035)	MeOH (35)	CH_3ONa (0.035, 1.0)	65	1.5	7.4 (88.3)	96.74	0.05	3.21
5	5 (0.017)	MeOH (50)	CH_3ONa (0.016,0.9)	0	48	3.25 (77.6)	98.55	-	1.45
6	5 (0.017)	MeOH (30)	CH_3ONa (0.017, 1.0)	0	48	3.55 (84.7)	99.35	0.09	0.48
7	5 (0.017)	THF (50)	CH_3ONa (0.019, 1.1)	25	30	3.2 (76.4)	92.48	0.10	7.44
8	5 (0.017)	Toluene (50)	CH_3ONa (0.019, 1.1)	25	30	2.8 (66.8)	94.76	0.20	4.86

(continued)

Ex No	DMAIA, g (mol)	Solvent, (ml)	Base, (mol, equiv.)	Temp., °C	Time, *h*	Crude yield g (%)	Purity, %	% of (III)	% of (IV)
9	5 (0.017)	DMSO (50)	CH_3ONa (0.019, 1.1)	25	30	3.2 (76.4)	98.23	0.44	-

Example 10 - Preparation of Moxonidine by reaction of DMAIA with 1.0 molar equivalent of potassium carbonate

[0045] A mixture of DMAIA (5 g, 0.0174 mol) and potassium carbonate (2.4 g, 0.0174 mol, 1.0 molar equiv.) in methanol (40 ml) was heated at 45-50° C for 18 hours. Then, the reaction mixture was cooled to ambient temperature and acetic acid (4 ml) and water (35 ml) were added. After stirring for half an hour, 25% solution of ammonium hydroxide (4 ml) was added and the mixture was stirred for one hour. A colorless precipitate was collected by filtration, washed with water and dried at 50°C overnight to give 3.8 g of crude Moxonidine in 90.7% yield, having a purity of 99.23% (by HPLC), containing 0.10% of impurity (III) and 0.67% of impurity (IV).

Examples 11-12

[0046] The same reaction, which is provided in example 10, was carried out using potassium carbonate in methanol at different reaction conditions, as depicted in Table 2.

Table 2 - *Preparation of crude Moxonidine by reaction of DMAIA with potassium carbonate*

Ex No	DMAIA, g (mol)	Solvent, (ml)	Base, (mol, equiv.)	Temp., °C	Time, *h*	Crude yield g (%)	Purity, %	% of (III)	% of (IV)
11	5 (0.017)	MeOH (40)	K_2CO_3 (0.017, 1.0)	65	3	3.8 (90.7)	99.0	1.0	-
12	5 (0.017)	MeOH (40)	K_2CO_3 (0.01,0.6)	65	4	3.4 (81.1)	99.33	0.6	0.07

Example 13 - Preparation of Moxonidine by reaction of DMAIA with 1.5 equivalents of 47% aqueous solution of sodium hydroxide

[0047] A mixture of DMAIA (5 g, 0.0174 mol) and 47% aqueous solution of sodium hydroxide (1.25 g, 0.026 mol, 1.5 equiv.) in methanol (40 ml) was stirred at 40-50°C for 10 hours. Then, the reaction mixture was cooled to ambient temperature and water (50 ml) was added. After stirring for one hour, a colorless precipitate was collected by filtration, washed with water (3 x10 ml) and 2-propanol (3 x10 ml) and dried at 50°C overnight to yield 3.7 g of crude Moxonidine in 88.3% yield, having a purity of 99.52% (by HPLC), containing 0.04% of impurity (III) and 0.44% of impurity (IV).

Examples 14 -16

[0048] The same reaction, which is provided in example 13, was carried out using sodium hydroxide solution in methanol at different reaction conditions, as depicted in Table 3.

Table 3 - ***Preparation of crude Moxonidine by reaction of DMAIA with sodium hydroxide solution***

Ex No	DMAIA, g (mol)	Solvent, (ml)	Base, (mol, equiv.)	Temp., °C	Time, *h*	Crude yield g (%)	Purity, %	% of (III)	% of (IV)
14	5 (0.017)	MeOH (40)	47% aq. NaOH sol. (0.019, 1.1)	25	24	3.7 (88.3)	98.54	-	1.46
15	5 (0.017)	MeOH (40)	47% aq. NaOH sol. (0.023, 1.3)	55-60	5	3.7 (88.3)	99.47	0.08	0.45
16	5 (0.017)	MeOH (40)	47% aq. NaOH sol. (0.019, 1.1)	65	2	3.4 (81.1)	98.86	0.13	1.01

Example 17 - Preparation of Moxonidine by reaction of DMAIA with 1.3 equivalents of 85% potassium hydroxide powder at ambient temperature

[0049] A mixture of DMAIA (5 g, 0.0174 mol) and 85% potassium hydroxide powder (1.5 g, 0.0226 mol, 1.3 equiv.) in methanol (40 ml) was stirred at ambient temperature for 24 hours. Then, water (50 ml) was added and the mixture was stirred for one hour. A colorless precipitate was collected by filtration, washed with water (3 x10 ml) and 2-propanol (3 x10 ml) and dried at 50°C overnight to give 3.7 g of crude Moxonidine in 88.3% yield, having a purity of 99.49% (by HPLC), containing 0.01% of impurity (III) and 0.50% of impurity (IV).

Examples 18 -19

[0050] The same reaction, which is provided in example 17, was carried out using 85% potassium hydroxide powder in methanol at different reaction conditions, as depicted in Table 4.

Table 4 - ***Preparation of crude Moxonidine by reaction of DMAIA with solid potassium hydroxide***

No	DMAIA, g (mol)	Solvent, (ml)	Base, (mol, equiv.)	Temp., °C	Time, *h*	Crude yield g (%)	Purity, %	% of (III)	% of (IV)
18	5 (0.017)	MeOH (40)	85% KOH powder (0.019, 1.1)	25	30	3.5 (83.5)	98.21	0.02	1.77
19	5 (0.017)	MeOH (40)	85% KOH powder (0.026, 1.5)	25	12	3.7 (88.3)	99.50	-	0.50

Example 20 - Preparation of Moxonidine by reaction of DMAIA with 45% aqueous potassium hydroxide solution at ambient temperature

[0051] A mixture of DMAIA (5 g, 0.0174 mol) and 45% aqueous potassium hydroxide solution (1.8 g, 0.029 mol, 1.7 equiv.) in methanol (40 ml) was stirred at ambient temperature for 10 hours. Then, water (50 ml) was added and the mixture was stirred for one hour. A colorless precipitate was collected by filtration, washed with water (3 x10 ml) and 2-propanol (3 x10 ml) and dried at 50° C overnight to give 3.7 g of crude Moxonidine in 88.3% yield, having a purity of

99.45% (by HPIC), containing 0.03% of impurity (III) and 0.52% of impurity (IV).

Examples 21 -25

[0052] The same reaction, which is provided in example 20, was carried out using aqueous potassium hydroxide in methanol at different reaction conditions, as deploted in Table 5.

Table 5 - *Preparation of crude Moxonidine by reaction of DMAIA with aqueous potassium hydroxide*

Ex. No	DMAIA, g (mol)	Solvent, (ml)	Base, (mol, equiv.)	Temp., °C	Time, *h*	Crude Yield g (%)	Purity, %	%of (III)	%of (IV)
21	5 (0.017)	MeOH (40)	45% aq. KOH sol. (0.023, 1.3)	65	3	3.6 (85.9)	99.34	0.19	0.47
22	5 (0.017)	MeOH (40)	45% aq. KOH sol. (0.019, 1.1)	65	2	3.4 (81.1)	98.28	0.20	1.52
23	5 (0.017)	MeOH (40)	45% aq. KOH sol. (0.023, 1.3)	25	11	3.6 (85.9)	98.71	0.01	1.28
24	5 (0.017)	MeOH (40)	45% aq. KOH sol. (0.026, 1.5)	25	10	3.6 (85.9)	99.04	0.02	0.93
25	5 (0.017)	MeOH (40)	45% aq. KOH sol. (0.029, 1.7)	25	10	3.7 (88.3)	99.17	0.02	0.81

Examples 26 -29

[0053] The same reaction, which is provided in example 17, was carried out using sodium bicarbonate powder in methanol, optionally with addition of small volume of water (example 29), at different reaction conditions, as depicted in Table 6.

Table 6 - *Preparation of crude Moxonidine by reaction of DMAIA with sodium bicarbonate*

Ex. No	DMAIA, g (mol)	Solvent, (ml)	Base, (mol, equiv.)	Temp., °C	Time, *h*	Crude Yield g (%)	Purity, %	% of (III)	% of (IV)
26	5 (0.017)	MeOH (40)	$NaHCO_3$ (0.017, 1.0)	65	14.5	3.6 (85.9)	98.71	0.56	0.65
27	5 (0.017)	MeOH (40)	$NaHCO_3$ (0.023, 1.3)	65	17.5	3.7 (88.3)	97.82	1.32	0.86

(continued)

Ex. No	DMAIA, g (mol)	Solvent, (ml)	Base, (mol, equiv.)	Temp., °C	Time, *h*	Crude Yield g (%)	Purity, %	% of (III)	% of (IV)
28	5 (0.017)	MeOH (40)	$NaHCO_3$ (0.026, 1.5)	40-50	24	2.9 (71.1)	97.85	1.87	0.14
29	5 (0.017)	MeOH (40), water (2)	$NaHCO_3$ (0.029, 1.7)	65	6	3.7 (88.3)	98.59	0.28	1.13

Examples 30 -31

[0054] The same reaction, which is provided in example 17, was carried out using potassium bicarbonate powder in methanol, optionally with addition of small volume of water (example 31), at different reaction conditions, as depicted in Table 7.

Table 7 - *Preparation of crude Moxonidine by reaction of DMAIA with potassium bicarbonate*

Ex. No	DMAIA, g (mol)	Solvent, (ml)	Base, (mol, equiv.)	Temp., °C	Time, *h*	Crude Yield g (%)	Purity, %	% of (III)	% of (IV)
30	5 (0.017)	MeOH (40)	$KHCO_3$ (0.026, 1.5)	65	9	3.6 (85.9)	99.39	0.53	0.08
31	5 (0.017)	MeOH (40), water (2)	$KHCO_3$ (0.026, 1.5)	65	10	3.7 (88.3)	99.20	0.35	0.45

Example 32 - Preparation of Moxonidine by reaction of DMAIA with a mixture of aqueous potassium hydroxide and solid potassium carbonate at ambient temperature

[0055] A mixture of DMAIA (5 g, 0.0174 mol) and 45% potassium hydroxide solution (0.023 mol, 1.3 equiv.) and solid potassium carbonate (0.004 mol, 0.2 equiv.) in methanol (40 ml) was stirred at ambient temperature for 16 hours. Then, water (50 ml) was added and the mixture was stirred for one hour. A colorless precipitate was collected by filtration, washed with water (3 x10 ml) and 2-propanol (3 x10 ml) and dried at 50° C overnight to yield 3.6 g of crude Moxonidine in 85.9% yield, having a purity of 99.07% (by HPLC), containing 0.03% of impurity (III) and 0.90% of impurity (IV).

Example 33 - Crystallization of Moxonidine from DMSO

[0056] Crude Moxonidine (2.0 g), having a purity of 99.12% and containing 0.03% of impurity (III) and 0.85% of impurity (IV), was mixed with DMSO (10 ml) and heated to a temperature of about 90°C to obtain a clear solution. The solution was cooled to ambient temperature and the thus formed crystals were obtained by filtration and washed with cold 2-propanol and dried under reduced pressure. 1.7 g of crystallized Moxonidine were obtained in 85% yield having a purity by HPLC of 99.91%, and containing 0.02% of impurity (III) and 0.06% of impurity (IV)

[0057] Table 8 contains the results of crystallization from different solvents.

Table 8. *Crystallization of crude Moxonidine from different solvents*

Ex. No.	Solvent	volume, ml	Moxonidine crude, g	Yield, %	Purity, %	% of (III)	% of (IV)
34	1-propanol	48	2	85	99.61	0.04	0.30
35	2-propanol	80	2	80	99.35	0.03	0.62
36	1-butanol	52	2	85	99.70	0.05	0.25

[0058] All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

[0059] The use of the terms "a" and "an" and "the" and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to,") unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring 20 individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as ") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[0060] Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art up6n reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

Claims

1. A process for preparing Moxonidine, comprising:

    reacting 4,6-dichloro-2-methyl-5-(1-acetyl-2-imidazolin-2-yl)amino-pyrimidine (DMAIA) with sodium methoxide at ambient temperature in an organic solvent;
    quenching the reaction mixture with water;
    isolating Moxonidine; and
    optionally recrystallizing Moxonidine from an organic solvent.

2. The process of claim 1, wherein between 0.9-1.7 equivalents of sodium methoxide are used with respect to 1 equivalent of DMAIA and the reaction is carried out at ambient temperature.

3. The process of claim 1, wherein the organic solvent is selected from the group consisting of methanol, tetrahydrofuran (THF), dimethyl sulfoxide (DMSO), and toluene.

4. The process of claim 1, wherein water is added to the reaction mixture after reaction completion, and the crude Moxonidine is isolated from the resulting suspension by filtration, washed with water and 2-propanol and dried.

5. The process of claim 1, wherein crude non-crystallized Moxonidine is obtained in at least 88% yield.

6. The process of claim 5, wherein crude non-crystallized Moxonidine is obtained in a yield higher than 90.5%.

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EUROPEAN SEARCH REPORT

Application Number
EP 08 01 2788

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
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Y	DE 29 37 023 A1 (BEIERSDORF AG) 2 April 1981 (1981-04-02) * pages 8,9 * * example 3 * -----	1-6	
Y	DE 28 49 537 A1 (BEIERSDORF AG) 22 May 1980 (1980-05-22) * pages 9,10 * * example 5 * -----	1-6	
Y	WO 2004/037795 A (DEGUSSA [DE]; HUBER SYLVIA [DE]; GUETHNER THOMAS [DE]; MOSER WOLFGANG) 6 May 2004 (2004-05-06) * page 2, line 26 - page 3, line 3 * * page 4, line 5 - line 14 * * examples 1-3 * -----	1-6	TECHNICAL FIELDS SEARCHED (IPC)
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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Munich	9 September 2008	Nikolai, Joachim

CATEGORY OF CITED DOCUMENTS

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